Long-term ex vivo haematopoietic-stem-cell expansion allows nonconditioned transplantation.

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Public Summary:

Scientific Abstract:
Multipotent self-renewing haematopoietic stem cells (HSCs) regenerate the adult blood system after transplantation(1), which is a curative therapy for numerous diseases including immunodeficiencies and leukaemias(2). Although substantial effort has been applied to identifying HSC maintenance factors through the characterization of the in vivo bone-marrow HSC microenvironment or niche(3-5), stable ex vivo HSC expansion has previously been unattainable(6,7). Here we describe the development of a defined, albumin-free culture system that supports the long-term ex vivo expansion of functional mouse HSCs. We used a systematic optimization approach, and found that high levels of thrombopoietin synergize with low levels of stem-cell factor and fibronectin to sustain HSC self-renewal. Serum albumin has long been recognized as a major source of biological contaminants in HSC cultures(8); we identify polyvinyl alcohol as a functionally superior replacement for serum albumin that is compatible with good manufacturing practice. These conditions afford between 236- and 899-fold expansions of functional HSCs over 1 month, although analysis of clonally derived cultures suggests that there is considerable heterogeneity in the self-renewal capacity of HSCs ex vivo. Using this system, HSC cultures that are derived from only 50 cells robustly engraft in recipient mice without the normal requirement for toxic pre-conditioning (for example, radiation), which may be relevant for HSC transplantation in humans. These findings therefore have important implications for both basic HSC research and clinical haematology.